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Trace elements as paradigms of developmental neurotoxicants: lead, methylmercury and arsenic

Philippe Grandjean^{a, b, *}, Katherine T. Herz^b

^a *Department of Environmental Medicine, University of Southern Denmark, 5000 Odense, Denmark*

^b *Department of Environmental Health, Harvard School of Public Health, Boston, MA 02215 USA*

*Corresponding author

P. Grandjean, University of Southern Denmark, J.B.Winslowsvej 17A, 5000 Odense, Denmark.

E-mail: PGrandjean@health.sdu.dk

Short title: Trace element neurotoxicity

Abstract

Trace elements have contributed unique insights into developmental neurotoxicity and serve as paradigms for such adverse effects. Many trace elements are retained in the body for long periods and can be easily measured for the purpose of exposure assessment by inexpensive analytical methods of analysis that became available several decades ago. Thus, past and cumulated exposures could be easily characterized from analysis of biological samples, such as blood and urine. Compelling evidence resulted from unfortunate poisoning events that allowed for the scrutiny of long-term outcomes of acute exposures that occurred during early development. This documentation was followed by prospective studies of child cohorts examined with sensitive neurobehavioral methods, thus leading to an understanding that the brain is uniquely vulnerable to toxic damage during early development. Lead, methylmercury, and arsenic thereby serve as paradigm neurotoxicants that provide a reference for other substances that may have similar adverse effects. Less evidence is available on manganese, fluoride, and cadmium, but experience from the former trace elements suggest that, with time, adverse effects are likely to be documented at exposures previously thought to be low and safe.

Keywords: Arsenic, cadmium, children, environmental exposure, fluoride, lead, manganese, methylmercury, neurotoxicity

Introduction

Increased exposures to trace elements can result in undesirable consequences for human health. The developing brain, as it turns out, happens to be a highly vulnerable target organ in this regard [1], and important insights into developmental neurotoxicity derive from epidemiological studies of human populations exposed to trace elements. A key advantage offered by trace elements in such studies is that valid methods for exposure assessment are widely available. Several trace elements are retained for years in the human body and are easy to measure in biological samples. Of additional importance, dramatic insight into trace element toxicity has occurred in connection with tragic incidents of mass poisonings. Observational clinical studies provided documentation on adverse effects resulting from exposures during early development. Fig. 1 shows our present understanding of developmental neurotoxicity symbolized as an iceberg. Trace elements account for about half of the industrial chemicals that have been well documented so far as developmental neurotoxicants – especially lead, methylmercury, and arsenic. This review will highlight the lessons learned from research on human health consequences of trace element toxicity affecting brain development.

One early insight arose from the discovery of fetal toxicity, thus proving the failure of protection by the placenta that had been traditionally assumed [2]. This physiological insight was dramatically illustrated in the 1950s in Minamata, Japan, where pregnant women were unharmed by methylmercury exposure, while sufficient doses had passed the placenta to result in congenital poisoning of the infant [3]. The consequences of such exposures can be serious and long-lasting, as we only have one chance to develop a brain [4]. Complex developmental processes include cell multiplication, differentiation, migration, and generation of connections, and all of them must happen in a certain sequence and at a particular time. These processes are

uniquely sensitive to adverse effects caused by neurotoxic chemicals, such as lead and methylmercury. Due to the limited opportunities for repair and compensation, any damage that occurs to a brain of a fetus or child will likely remain for the rest of his/her life. The consequences can therefore be dire, and the global occurrence of these adverse effects have recently been termed a “silent pandemic” [5]. Thus, toxic chemicals are thought to contribute to neurodevelopmental delay and neurological disease that occur in about one of six children in the US [6].

The three trace elements that have resulted in the most important insights are lead, mercury (methylmercury), and arsenic. They are also prime examples – or paradigms – of environmental chemicals, for which the development of exposure standards and policies can be followed over time and linked to expanding research and growth of the knowledge base.

Lead

Lead has been utilized for thousands of years in numerous applications, many of which resulted in environmental dissemination and human exposures. Traditionally, lead poisoning was thought of as a potentially life-threatening disease, which, in survivors, left no trace. This illusion was exposed when two pediatricians traced twenty lead-poisoned children who had at first been discharged from hospital as “recovered” [7]. Nineteen of the children had severe learning or behavioral problems and were school failures, and only five had an IQ in the normal range. More than thirty years later, a landmark study showed that increased lead exposure was a major predictor of cognitive and behavioral problems in school children in Boston [8]. This study determined the lead content of deciduous teeth as a marker of cumulated lead exposure. With time, adverse effects were documented at lower and lower lead exposures, often documented by serial blood-lead determinations. These studies took advantage more sophisticated

epidemiological designs, they included larger groups of children and applied more sensitive tests of brain functions [9]. Recently, a subgroup of subjects from the original study of Boston school children was re-examined [10]. The 43 adults, now in their late 20s, had IQ scores that were inversely associated with their childhood lead exposure. This finding echoes what Byers and Lord said more than 50 years ago: Lead toxicity does not fade away.

Gradually, the general attitude began to change, and lead toxicity increasingly was recognized as a global risk to brain development. In 2010 the European Food Safety Authority (EFSA) evaluated the cumulative evidence, at the request of the European Commission [11]. The dispassionate conclusion reads, “It was not possible to exclude a risk to the developing fetus through exposure of some pregnant female consumers”. Despite the hedged language, this report represents a radical diversion from classical toxicology: There is no known safe exposure to lead, EFSA said. Soon thereafter, the conclusion that no blood lead concentration can be considered safe was echoed by other health authorities [12].

Given the discoveries on lead poisoning early in the previous century and even before that, one may wonder why it took so long for us to realize that lead exposure can harm brain development. Part of the answer is that the medical and scientific establishment was not ready to consider “subclinical” effects a true public health hazard [13]. Another part of the answer is that large, prospective studies using sophisticated tests only became possible from the 1970s onwards. For example, modern imaging techniques have only recently allowed documentation of reductions in gray matter (cortex) volume, especially of the prefrontal cortex in adults with increased childhood lead exposures [14].

But there is a third issue that hampered scientific insight into lead toxicity. Since ancient times, lead had been looked upon as a highly useful metal. Given its economic value, any claims that

lead might be toxic were not taken on face value. When lead additives were introduced as effective octane-boosters for gasoline in the 1920s, spokesman for the lead industry, Dr. Robert A. Kehoe explained that industry leaders would make responsible decisions, but only when justified: “They have expressed themselves repeatedly not so much as being interested in opinions as being interested in facts, and if it can be shown... that an actual danger to the public [occurs] as a result of the treatment of the gasoline with lead, the distribution of gasoline with lead in it will be discontinued from that moment” [15]. Summing up the argument, he added: “It is a thing which should be treated solely on the basis of facts”. Later referred to as Kehoe’s show-me rule, his stance was strictly adhered to during subsequent decades so that very little would be accepted as a “fact”, unless it was in favor of the continued use of lead additives. The mere notion that a chemical substance should be considered innocuous, unless proof of the opposite could be obtained, is of course not logical, and the consequences if proven otherwise detrimental to public health.

Even today, lead exposure causes neurodevelopmental deficits that are associated with losses of IQ points [16], impaired school performance [17], and associated very substantial economic losses to society [18, 19]. Thus, even though lead toxicity is widely recognized today, its adverse effects still occur as a result of reckless applications of lead in the past and our unwillingness to accept that a useful metal could be so harmful. Although lead’s persistence in the body allowed for reliable exposure assessment from blood analyses, this very property is also the cause of the lasting difficulties in properly controlling human exposures.

Methylmercury

Unlike lead, methylmercury (MeHg) is not used for any industrial purposes and originates from methylation of inorganic mercury in sediments from where it accumulates in aquatic food chains.

MeHg may also be formed from industrial uses of mercury as a catalyst, as happened at the Chisso factory in Minamata, Japan [20]. Worldwide exposure to MeHg comes from consumption of fish and seafood, but poisoning episodes have also been caused by past uses of MeHg as a fungicide to treat seed grain [21]. The poisoning episodes in Japan, Iraq, and other countries clearly documented that an exposed mother could escape unscathed, while her child might suffer serious mental retardation caused by the MeHg [3]. Still, the extent of these mass poisonings was never fully revealed, as the official statistics were incomplete and relied on documentation of severe clinical adverse effects.

Inspired by the documentation of more subtle neurodevelopmental effects due to lead exposure, prospective studies were then initiated to determine if maternal consumption of contaminated seafood during pregnancy might represent a hazard to prenatal brain development. In this case, the mother's hair-mercury was first used as a marker of the exposure [22], and more accurate estimates were later obtained from analyzing cord blood for mercury [23]. Neurodevelopment was assessed by IQ scales and neuropsychological tests. In a review of the evidence available by 2000, the U.S. National Research Council concluded that MeHg was a developmental neurotoxicant, and that an exposure limit should aim at preventing this risk [24]. A few years later, when an international expert committee for the fourth time evaluated MeHg, it finally agreed that the developing fetus is more vulnerable than the adult, although the committee decided on a limit more than twice the magnitude of the U.S. limit [25].

Again in regard to MeHg, scientific evidence appeared with a delay, but public policy decisions were even more delayed. Suppression of data occurred, but the main problem was that the initial focus was on the uncertainties in epidemiological studies, where exposures are not a matter of design and therefore involve measurement uncertainty. Less attention was paid to the question

what could have been known, given the research methods and possibilities, and whether developmental neurotoxicity at low doses could be ruled out [3]. The reports also generally ignored that imprecision of the exposure assessment most likely resulted in an underestimation of the true effects [26].

One of the confounding variables was the beneficial effects on brain development caused by essential nutrients present in seafood along with the MeHg, one important nutrient being a trace element [27]. In this case, seafood components resulted in effects in opposite directions, so that so-called negative confounding occurred [28]. This was the case in a prospective study in the Seychelles [29] that had been hailed as “proof” that MeHg from marine fish was not toxic [30]. In contrast, in the Faroe Islands, where another birth cohort was being followed, the MeHg mainly originated from pilot whale meat [31], which is of less importance as a source of essential nutrients. Even then, some negative confounding occurred in this population, so that even the initial dose-response relationship underestimated the MeHg toxicity [32].

This problem of negative confounding has still not been entirely resolved. Thus, in its most recent opinion on MeHg from 2012, EFSA deviated from other risk assessments by recognizing neurodevelopmental toxicity only when it exceeded the advantages associated with seafood nutrients [33]. Thus, this expert group weighed the tolerable weekly intake of MeHg exposure against the gain of beneficial nutrients present in the same food items. Unfortunately, this decision allows for simultaneous quenching of the benefits from these nutrients, and EFSA does not justify why a decreased benefit from a healthy diet due to MeHg should be considered acceptable. A more appropriate decision would be to maximize the benefits by minimizing the toxicant exposure.

Despite any remaining uncertainties, international agreement has been reached on the necessity to control mercury pollution, and in 2013, the Minamata Convention was signed by United Nations member states [34]. Still, due to the persistence of MeHg in the aquatic environment, contamination of seafood is not going to decrease in the near future. There is therefore a need to monitor the occurrence of elevated MeHg exposures in women who are or plan to be pregnant so that prenatal toxicity can be prevented.

Arsenic

A third neurotoxic trace element is arsenic. Knowledge on its developmental neurotoxicity emerged in connection with a dramatic poisoning incident in Japan [35]. In the summer of 1955, an unusual disease occurred in the western part of the country, with anorexia, diarrhea, vomiting, abdominal distention, fever, and skin pigmentation among hundreds of infants. The majority of the sick infants were bottle-fed, and those who were breastfed had also received milk supplement. It soon turned out that Morinaga milk powder was the common source. The contamination was traced to impure disodium phosphate added as a stabilizer to the powdered cow's milk; the phosphate additive turned out to contain 5-8% of arsenic. Using strict diagnostic criteria, as in the case of MeHg, a governmental committee reported a total of 12,000 victims and a 1% mortality rate, but the true numbers may have been substantially higher if counting infants with less dramatic clinical signs [4]. Again, adults exposed to the contaminated milk powder exhibited much less serious toxicity. As with lead, patients were considered cured after the acute toxicity had faded.

Follow-up of Morinaga patients was not carried out for several years, in part because the responsible company was unwilling to support such research. However, teenagers who had suffered poisoning as infants were later examined and showed deficits on IQ scores and an

increased prevalence of central nervous system disorders, including mental retardation and epilepsy [35]. Very limited follow-up has been carried out since then, so little is known on the long-term neurobehavioral consequences of developmental arsenic neurotoxicity.

In a completely different scenario, millions of children and pregnant women are exposed to arsenic from contaminated drinking water. The most serious problem began in the 1970s when thousands of water wells were dug in Bangladesh and the West Bengal in India to avoid pathogenic bacteria. Serious arsenic contamination of the groundwater also occurs elsewhere from Pakistan to China, and in many other countries of the world, where eroding minerals release arsenic to the water as a result of oxidation processes.

During recent years, evidence has emerged that children with increased exposure to arsenic suffer neurodevelopmental deficits [36], including children exposed from metallurgic industries [37]. In contrast to lead and MeHg, where validated techniques are available for exposure assessment, long-term arsenic exposure is much more difficult to determine and must rely on changeable concentrations in urine samples [38]. For this reason, the epidemiological evidence is not yet as solid in regard to neurotoxic risks at commonly occurring arsenic exposures [39, 40].

Perspective

Lead, methylmercury, and arsenic were among the first human developmental neurotoxicants to be discovered, and much of what we know today on neurodevelopmental toxicity either originates from documentation on these trace elements or was inspired by early findings relating to these substances. Uncertainties were apparent, but biases toward the null were often ignored, and adverse effects were more likely to be underestimated than the opposite. Adding to this imbalance, scientific reports were often hedged and included numerous caveats and disclaimers,

thus paving the way for vested interests to dispute or discredit the findings and for regulatory agencies to delay the translation into public policy and prevention [41].

Other trace elements also appear to cause neurodevelopmental toxicity. Manganese is another water contaminant, and cross-sectional data from Bangladesh show that it is associated with decreased mathematics achievement scores in school children [42]. School-aged children living near manganese mining and processing facilities have shown associations between airborne manganese levels and impaired motor skills and diminished olfactory function [43]. Likewise, cadmium has been implicated as a neurotoxic co-factor in children with mixed-metal exposures [44]. Perhaps more worrying is the evidence that increased exposure to fluoride can cause neurotoxicity in children. Most of this evidence has been gathered in China, where the overall agreement between studies and the apparent lack of any serious confounding support the notion that fluoride is a developmental neurotoxicant [45]. Both manganese and fluoride are likely essential trace elements, and the findings of adverse effects on brain development therefore illustrate the fact that even essential trace elements may be toxic.

The evidence and the acceptance of the new knowledge did not develop overnight and was in fact delayed by decades. Fig. 2 shows the general pattern of recognition with time, where neurotoxicity was first documented in adults, later on in children, often in connection with poisoning events. Then followed in-depth studies of childhood populations, where more subtle adverse effects were discovered. For lead, methylmercury, and arsenic, the evidence available today clearly shows that these trace elements are contributing to the “silent pandemic”. Less evidence is available on manganese, fluoride, and cadmium, but experience from the previously mentioned trace elements suggest that, with time, adverse effects are likely to be documented at exposures previously thought to be low and safe.

Although solid and growing evidence is now available on several trace elements, the overall impact of developmental neurotoxicity caused by industrial chemicals is unknown due to the lack of systematic data on neurotoxic potentials. Given that data quality may be far from ideal, that too few subjects have been followed for too short a time, and other limitations, epidemiology can only provide insight into causal associations to the extent allowed by the underlying information. In addition to critical scrutiny of an epidemiological study, the full perspective also needs to be appreciated: What is it possible to know at this point in time, given the types of data that are accessible for epidemiological study of neurodevelopmental toxicity?

The societal implications are substantial. Developmental neurotoxicity results in lasting cognitive deficits and may also cause behavioral abnormalities. In regard to cognition and associated educational achievements, economists have calculated the forgone lifetime income in terms of discounted present-day value [19]. The amounts are huge and illustrate the importance to rely not only on formal medical diagnoses as a relevant outcome, but also to consider functional deficits of the brain. In this perspective, current prevention efforts in regard to trace elements known to be neurotoxic are insufficient.

Additional trace elements and many other industrial chemicals may well constitute a hazard to human brain development [4]. Test methods to detect neurotoxicity are available, including in vitro tests that are inexpensive and rapid. Although some tests may need further validation, they are ready to be used to identify substances that are suspect. Trace element research has documented the consequences and the need to protect the brains of the next generation.

Conflict of interest

None declared.

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Legends to figures:

Figure 1. For developmental neurotoxicants, the evidence first dealt with adverse effects at high doses on the adult nervous system, later followed by case reports and epidemiological evidence on developmental toxicity at successively lower doses, to which childhood populations of increasing magnitude are exposed. Trace elements provided some of the first evidence and followed this curve towards the upper right, with the evidence on manganese and fluoride being somewhat delayed in comparison with lead, methylmercury (MeHg), and arsenic. Revised from Grandjean and Landrigan [5].

Figure 2. Of the thousands of chemicals in current use, only a small fraction has been documented to cause developmental neurotoxicity in humans. Trace elements represent about half of the substances now known to cause developmental neurotoxicity in humans, as tip of the iceberg. Trace elements also contribute to the list of chemicals that are known to cause clinical neurological effects. Such effects are must less clear and remain poorly studied in regard to other industrial chemicals. Revised from Grandjean and Landrigan [5].

